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Computational neuroscience meets optogenetics: Unlocking the brain's secrets

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Prof Simon Schultz and Dr Konstantin Nikolic

Computational neuroscience meets optogenetics:

Unlocking the brain's secrets

Working at the interface between engineering and neuroscience, Professor Simon Schultz and Dr Konstantin Nikolic at Imperial College London are developing tools to help us understand the intricate workings of the brain. Combining a revolutionary technology – optogenetics – with computational neuroscience, the team are developing powerful tools to study the real-time physiology of individual neurons and their function. Their work is unlocking the complex secrets of the circuitry of the brain and has significance for debilitating neural disorders such as Alzheimer's disease.

Composed of billions of specialised nerve cells (called neurons) wired together in complex, intricate webs, the brain is inherently challenging to study. Neurons communicate with each other by transmitting electrical and chemical signals along neural circuits: signals that vary both in space and time. Until now, technical limitations in the available research methods to study the brain has meant that we are a long way from understanding how information is represented and processed by neural circuits responsible for perception, action and memory. But this is changing.

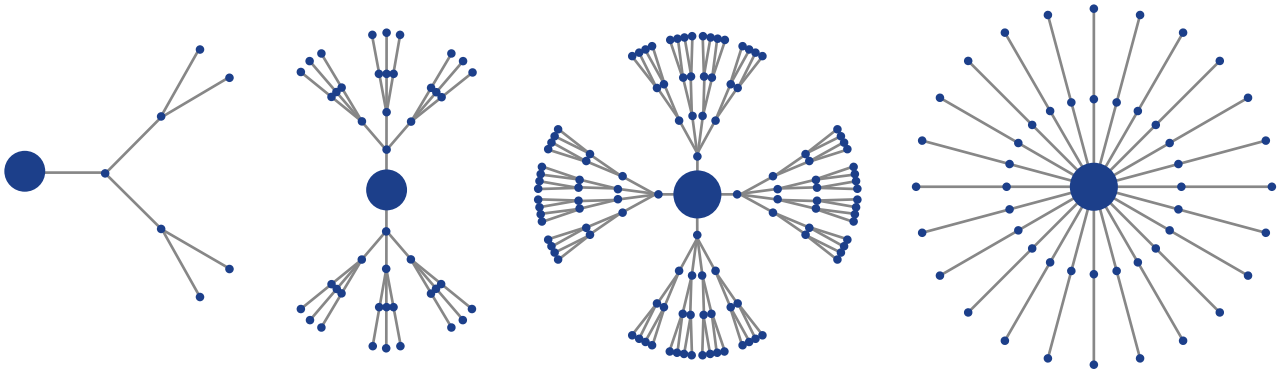
LET THERE BE LIGHT

A powerful new tool (invented by Boyden and Deisseroth just a little over a decade ago) allows researchers to map the brain's connections, giving unprecedented access to the workings of the brain. Its impressive resolution enables precise measurement of neural circuitry of living brain circuits in real-time. The technology, named optogenetics, makes use of light (optics) together with genetics (neurons that have been genetically sensitised to light). By shining a light on the genetically modified cells that are light-sensitive, researchers can switch them on or off. For the first time, the messages that neurons send to each other can be manipulated with a sophistication that mimics naturally occurring neural activity. By disturbing the activity of individual neurons, their effect on the system can be studied – something that could not have been envisaged several decades ago. This revolutionary methodology enables researchers to establish causal relationships between nerve-circuit activity and function, rather than merely observing correlations between the two.

A powerful new tool allows researchers to map the brain's connections, giving unprecedented access to the workings of the brain.

OPTOGENETICS MEETS COMPUTATIONAL NEUROSCIENCE

Charting new territories in neuroscience, researchers at Imperial College London are taking this revolutionary technology a step further. Simon Schultz, Professor



Simplified models allow researchers to study how the geometry of a neuron's "dendritic tree" affects its ability to process information.

of Neurotechnology and Director of the Imperial Centre of Excellence in Neurotechnology, Dr Konstantin Nikolic, Associate Professor in the Department of Electrical and Electronic Engineering, and Dr Sarah Jarvis are taking a unique approach: combining optogenetics with computational modelling. Although optogenetics has been applied to the field of neuroscience, computational modelling of the brain has not taken this new tool onboard. With this truly multidisciplinary approach, the Imperial researchers have developed a sophisticated computational optogenetic tool. Prof Schultz is widely known for his work on neural coding, which explores the core principles that underlie information processing in biological nervous systems. The key aspect to their current study is that for the first time in computational neuroscience, models of opsins are incorporated with detailed multi-compartment models of neurons: in essence, 'reverse engineering' the information processing architecture of the brain. Using optogenetic tools, the team can test the predictions made by their models directly, rather than indirectly. They are particularly interested in changes in cortical circuit properties during dementias such as Alzheimer's disease. Prof Schultz explains: 'I believe that understanding the functional principles of cortical circuits is crucial to understanding, and treating, the effects of brain disorders'.

SHEDDING LIGHT ON THE BRAIN

Their innovative approach uses sophisticated two-photon microscopy, optogenetics and electrophysiology to measure (and disturb) patterns of neuronal activity in vivo (in living tissue). Combining these experiments with theoretical work allows the team to tease apart and understand the data that they generate. On the theoretical side, the team develops algorithms for analysing the data and models to help interpret it.

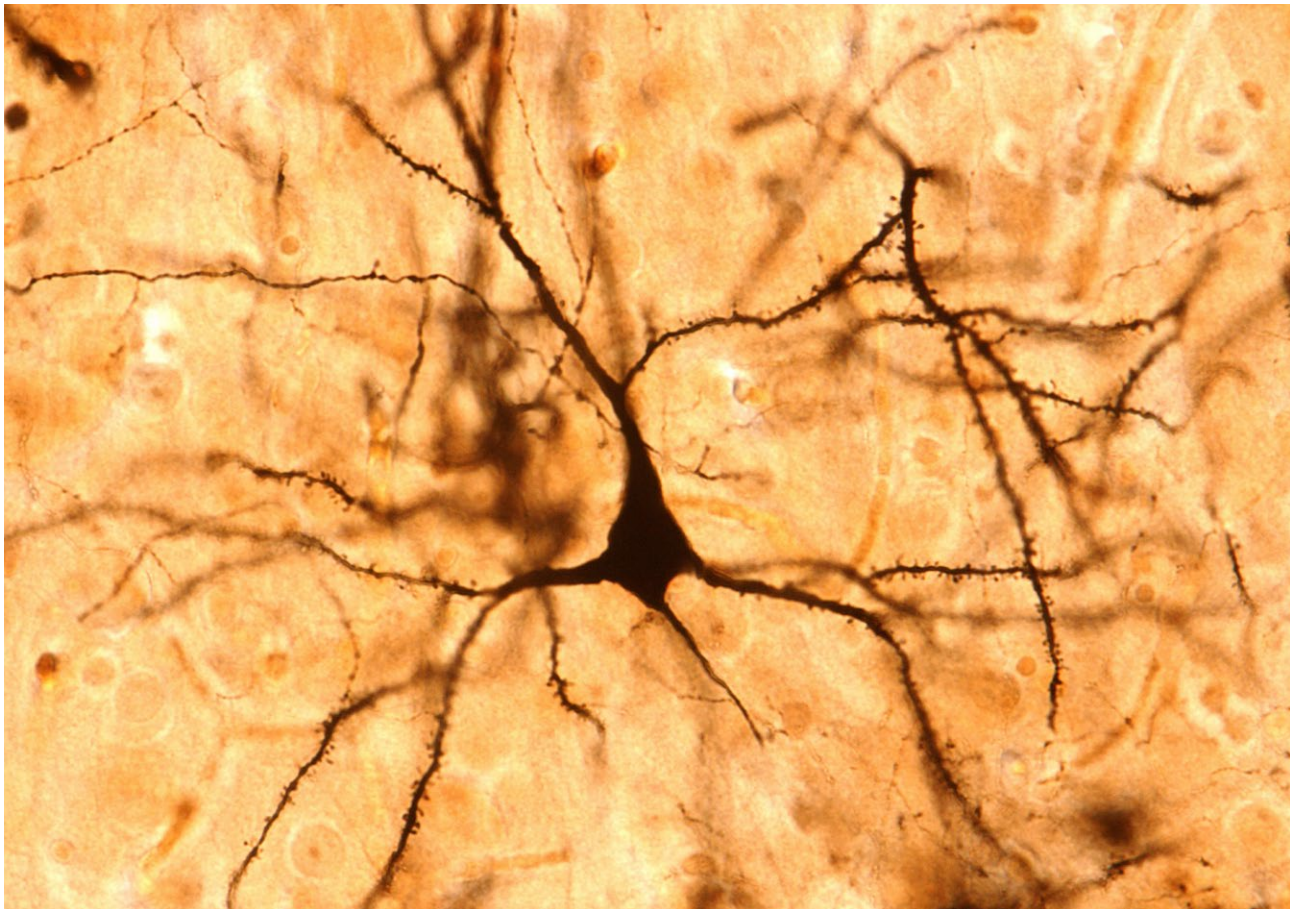
In a recently published study, the team explored one of the basic principles of information processing in neural (or cortical) circuits, called 'neural gain control.' Specifically, they were interested in ways that the gain (slope) of a neuron's input-output function can be modulated. Neural gain can be thought of as an amplifier of neural communication. When gain is increased, excited neurons become even more active; conversely, when gain is inhibited neurons become less active. As Prof Schultz explains: 'an important property of a neuron is, using engineering terminology, its 'gain'. That is, the slope of its input/output function, or the extent to which it amplifies its inputs'.

This ground-breaking research is helping refine our understanding of the modulation of individual nerve cells and how this may relate to different aspects of neural circuits.

AN INSIGHT INTO NEURONAL GAIN

Using two biophysical models of neurons, genetically-modified to include two distinct light-sensitive proteins (called opsins): channelrhodopsin-2 (ChR2) or halorhodopsin (NpHP), Prof Schultz and team could either induce or inhibit the connections between neurons (their synaptic activity). Using light to probe the cells, the researchers explored the extent to which a neuron's shape (its morphology) affects the level to which its gain can be controlled.

Most nerve cells have branched extensions called dendrites (rather like branches of a tree) that propagate the electrochemical messages from other cells to the cell body (soma). In their study, by measuring the effect that different ratios of the excitatory and inhibitory opsins have when experimentally placed in different parts of the neuron, the team were able to directly investigate the effect that the cell's shape has on gain. The team investigated four common types of dendritic shape and demonstrated that the arrangement of the dendrites is an important factor in controlling gain (either naturally, by neuromodulation, or artificially, using optogenetics). The symmetry of the dendrites relative to the soma (cell body) was also found to be important. The Imperial researchers thus showed that the structure of an individual neuron is key to its functional role within the network.



The shape of the cell's arms or 'dendrites' affects the neuronal gain.

The researchers showed that one common cell type in particular – the pyramidal cell – is highly modulable. Their finding reinforces our current understanding that the role of pyramidal cells within neural circuits is to act not only as the primary excitatory neuron but also as a key element for setting the gain of the circuit. Other cell types investigated by Prof Schultz and his team were found to be less modulable. This suggests that although these other cell types have important roles within the neural circuit, the gain of their input-output functions is unlikely to be modulated in vivo. They put forward the idea that it is likely that these cells experience shifts in overall excitability through changes in the amount of excitation or inhibition.

For the first time in computational neuroscience, models of opsins are incorporated with detailed multi-compartment models of neurons.

UNDERSTANDING THE BRAIN – A WORK IN PROGRESS

The potential for computational optogenetic modelling is vast. It is likely to impact on many areas of study, helping to bridge the gap between computational and experimental studies. Excitingly, it could be harnessed to extend the ability of neuroprosthetics – devices that connect to brain cells to deliver information that a diseased cell can no longer receive on its own, for example. As Prof Schultz explains: 'the potential for a new type of optical neuroprosthesis – one where, rather than just optically stimulating cells and making them fire (in effect over-writing what they otherwise might have said), the gain of the cell's input/output function is instead changed.' In essence, the tool enables researchers to adjust the sensitivity of a cell's response to its inputs, while at the same time preserving its ability to process information coming in. It is conceivable that this could allow development of an 'attentional prosthesis'. That is, make a specific set of neurons more sensitive to their inputs, rather than over-writing neural activity with new information.

ILLUMINATING RESEARCH

Using powerful new technology to manipulate individual neuronal circuits with sophisticated spatial and temporal accuracy, the team's ground-breaking research is helping refine our understanding of the modulation of individual nerve cells and how this may relate to different aspects of neural circuits. A better understanding of this, our most complex and most precious organ, may help us understand the dysfunction behind neurodegenerative disorders such as Alzheimer's disease, and has the potential to lead to effective treatments for many neurological conditions.

Behind the Research

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Research Objectives

Prof Schultz and Dr Nikolic combine the relatively new field of optogenetics with computational neuroscience to understand how the 'gain' of a neuron's input/output system is modulated.

Detail

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Collaborators

- Sarah Jarvis

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Personal Response

Your research holds promise for unravelling the complexities behind disorders of the brain and to develop new treatments. How far are we from achieving this?

"Progress on understanding and treating brain disorders is at the moment being limited, in my view, by our relatively poor understanding of how brain circuits process information, how that leads to behaviour, and of course how these circuits are perturbed in disease states. It is that "circuit-level" understanding that is crucial for further progress on problems such as neurodegenerative and neurodevelopmental disorders. In one sense, the brain is extremely complex, and we are still a long way off any kind of complete understanding. However, there have been tremendous advances in neurotechnology in the last decade – from new ways to image brain activity at cellular level, to new ways to alter activity in neural circuits with potential therapeutic applications, to ways to deliver drugs across the blood-brain barrier into targeted brain areas. I am thus optimistic that in the next decade we will see substantial progress in the development of new treatments for brain disorders."